

# Effect of Duodenal–Jejunal Exclusion in a Non-obese Animal Model of Type 2 Diabetes

## *A New Perspective for an Old Disease*

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**Background:** The Roux-en-Y gastric bypass and the biliopancreatic diversion effectively induce weight loss and long-term control of type 2 diabetes in morbidly obese individuals. It is unknown whether the control of diabetes is a secondary outcome from the treatment of obesity or a direct result of the duodenal–jejunal exclusion that both operations include. The aim of this study was to investigate whether duodenal–jejunal exclusion can control diabetes independently on resolution of obesity-related abnormalities.

**Methods:** A gastrojejunal bypass (GJB) with preservation of an intact gastric volume was performed in 10- to 12-week-old Goto-Kakizaki rats, a spontaneous nonobese model of type 2 diabetes. Fasting glycemia, oral glucose tolerance, insulin sensitivity, basal plasma insulin, and glucose-dependent-insulinotropic peptide as well as plasma levels of cholesterol, triglycerides, and free fatty acids were measured. The GJB was challenged against a sham operation, marked food restriction, and medical therapy with rosiglitazone in matched groups of animals. Rats were observed for 36 weeks after surgery.

**Results:** Mean plasma glucose 3 weeks after GJB was  $96.3 \pm 10.1$  mg/dL (preoperative values were  $159 \pm 47$  mg/dL;  $P = 0.01$ ). GJB strikingly improved glucose tolerance, inducing a greater than 40% reduction of the area under blood glucose concentration curve ( $P < 0.001$ ). These effects were not seen in the sham-operated animals despite similar operative time, same postoperative food intake rates, and no significant difference in weight gain profile. GJB resulted also in better glycemic control than greater weight loss from food restriction and than rosiglitazone therapy.

**Conclusions:** Results of our study support the hypothesis that the bypass of duodenum and jejunum can directly control type 2 diabetes and not secondarily to weight loss or treatment of obesity.

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These findings suggest a potential role of the proximal gut in the pathogenesis of the disease and put forward the possibility of alternative therapeutic approaches for the management of type 2 diabetes.

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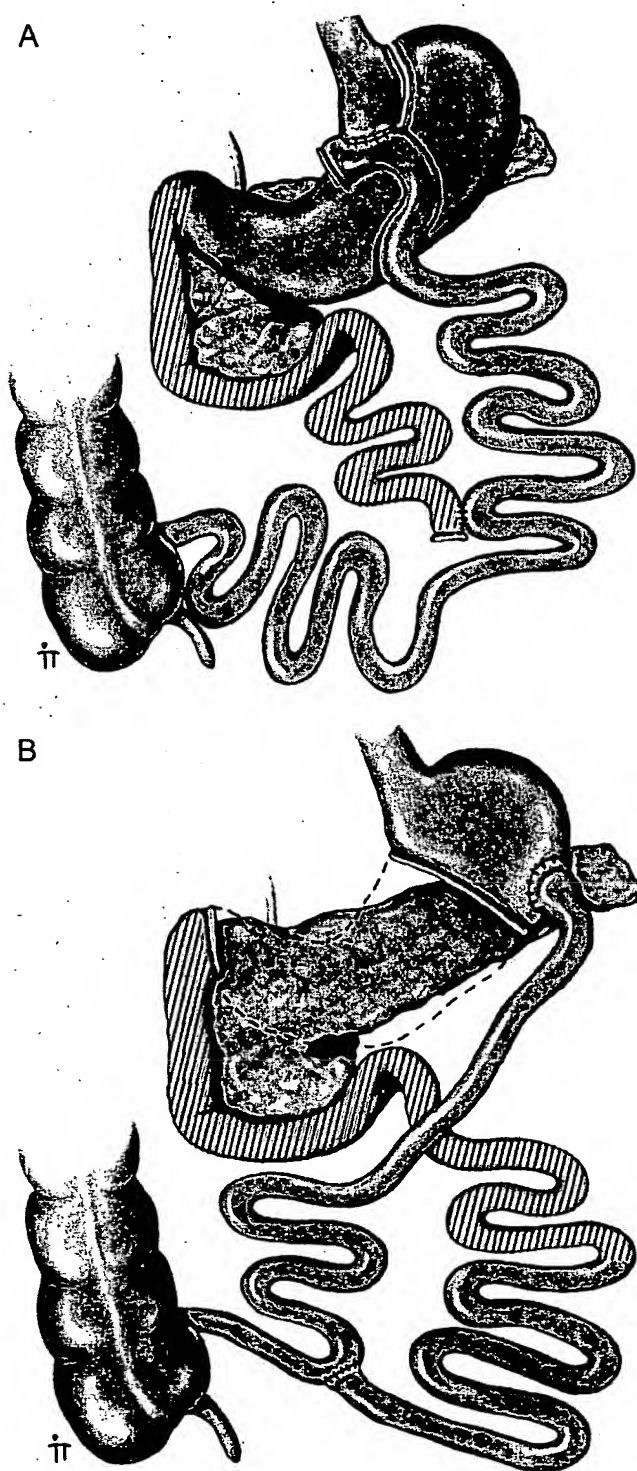
Diabetes mellitus presently affects more than 150 million people worldwide,<sup>1</sup> a number expected to double by the year 2025.<sup>2</sup> More than 90% of patients suffer from the type 2 form,<sup>3</sup> a progressive disorder associated with life-threatening complications and whose etiology remains still elusive.

The resolution of type 2 diabetes has been observed as an additional outcome of surgical treatment of morbid obesity (body mass index [BMI]  $>40$  kg/m<sup>2</sup>).<sup>4</sup> Two procedures, the Roux-en-Y gastric bypass (RYGBP) and the biliopancreatic diversion (BPD), are more effective treatments for diabetes than other procedures<sup>5</sup> and determine normal concentrations of plasma glucose, insulin, and glycosylated hemoglobin in 80–100% of morbidly obese patients.<sup>6–9</sup> Because BMI is the dominant risk factor for diabetes<sup>10,11</sup> and weight loss and hypocaloric diet reduce plasma glucose and improve insulin sensitivity in obese individuals,<sup>12</sup> this antidiabetic effect of surgery has been interpreted as a conceivable result of the surgically induced weight loss and decreased caloric intake.<sup>13</sup>

Glycemic control, however, often occurs within days, long before significant weight loss,<sup>7,14,15</sup> suggesting that the control of diabetes may be a direct effect of the operations rather than a secondary outcome of the amelioration of obesity-related abnormalities.

Both the RYGBP and the BPD include, among other elements, the bypass of the duodenum and part of the jejunum (Fig. 1). Because several peptides released in this part of the bowel are involved in governing beta-cell function both in physiological<sup>16</sup> and diabetic states,<sup>17,18</sup> changes in the entero-insular axis might explain their antidiabetic effect.

We speculated that if the control of diabetes is not a secondary outcome of the treatment of obesity but, rather, a direct effect of duodenal–jejunal exclusion, then similar re-



**FIGURE 1.** Roux-en-Y gastric bypass (A) includes creation of a small gastric pouch while the jejunum is divided 30–50 cm distal to the ligament of Treitz. The distal limb of the jejunum is then anastomosed to the small gastric pouch and a jejunojunosotomy is performed 50 to 150 cm distal from the gastrojejunostomy. The biliopancreatic diversion (B) includes resection of the

distal stomach and diversion of the biliopancreatic juices to the terminal ileum, 50 to 100 cm proximally to the ileocecal valve. The 2 operations thus have in common the exclusion of duodenum and proximal jejunum from the transit of food.

## MATERIALS AND METHODS

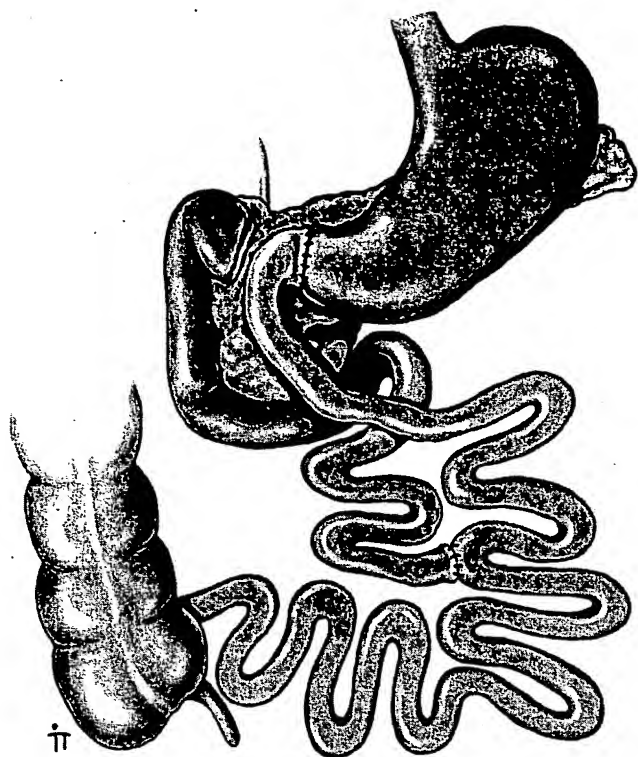
### Animals and Chow Diet

Male GK rats who were 6–8 weeks of age were purchased from Taconic M&B A/S (Denmark). Animals had free access to tap water and were ad libitum fed with a 5% fat rat chow diet (Altromin 13/14). The study was approved by the Institutional Animal Care Committee of the IRCAD-EITS of Strasbourg, France.

### Experimental Protocol

After the rats were acclimated for 1 week, food intake weight, fasting glycemia, and oral glucose tolerance were measured. Then, in a first set of experiments, 10- to 12-week-old rats randomly underwent one of the following: 1) gastrojejunum bypass (GJB), 2) sham operation, 3) food restriction, or 4) no intervention (controls). All groups were fed the same type of diet. In GJB and sham-operated animals, postoperative measurements of fasting glycemia were performed at several time points for a total follow-up of 36 weeks. Oral glucose tolerance was measured 1 week, 2 weeks, 1 month, and 36 weeks after surgery. Fasting plasma insulin and glucose-dependent-insulinotropic peptide (GIP) were measured before and 2 weeks after surgery. Measurement of plasma lipids and insulin tolerance test (ITT) were performed in GJB rats and sham operated animals 20 weeks postoperatively. Age-matched nondiabetic animals (Wistar rats) fed ad libitum the same rat chow for a minimum of 20 weeks were used as normal controls for plasma lipidic profile.

A second set of experiments was performed to compare the effect of GJB to that of the insulin-sensitizing drug rosiglitazone. GK rats who were 8 weeks old were randomly assigned to: 1) GJB, 2) rosiglitazone treatment, or 3) no intervention (controls). Fasting glycemia, oral glucose tolerance test (OGTT), and ITT were tested 1 week after GJB and at the end of the 10-day period of rosiglitazone therapy.



**FIGURE 2.** Gastrojeunal bypass. The duodenum was separated from the stomach, and bowel continuity was interrupted at the level of the distal jejunum, (8 cm from the ligament of Treitz). The distal of the 2 limbs was directly connected to the stomach (gastrojeunal anastomosis) and the proximal limb carrying the biliopancreatic juices was reconnected downward to the alimentary limb at a distance of 12 cm from the gastrojeunal anastomosis (Roux-en-Y reconstruction)

## Interventions

Rats undergoing either GJB or the sham operation were fasted overnight and anesthetized with 2% isoflurane and air/oxygen.

For GJB, the gastric volume was maintained intact while the entire duodenum and the proximal jejunum were bypassed. The details of the procedure are illustrated in Figure 2.

For the sham operation, transections and reanastomosis of the gastrointestinal tract were performed at multiple sites (corresponding to where enterotomies were performed for the GJB), but the physiologic circuit of food was maintained through the bowel. When needed, operative time was prolonged to produce a similar degree of anesthesiological stress as those rats who received GJB.

Food intake restriction consisted of the following: after measuring the mean daily food intake for 2 weeks in a matched and ad libitum-fed group of rats, access to food was then restricted to only one third of the original amount for 3 consecutive weeks.

Finally, rosiglitazone (Avandia™, SmithKline Beecham, Thorishaus, Switzerland) was administered through the drinkable water for 10 days at an intentional dose of 15 mg/kg/day. The actual dose was calculated by daily measurement of drunken water and body weight. This regimen was chosen based on previous reports documenting improved insulin sensitivity in rat models of type 2 diabetes with as low as 3 mg/kg/day of rosiglitazone for 7 days.<sup>20</sup>

## Measurements

Weight and food intake were measured daily for the first 2 weeks after the intervention, twice a week for the following 2 weeks, and then monthly for 3 months after surgery.

For fasting glycemia, after a fasting period of 12–14 hours, blood was collected from the tail in conscious animals. Samples were centrifuged and plasma glucose analyzed using the glucose oxidase method (Roche/Hitachi 917, Roche Diagnostic, Mannheim, Germany).

For OGTT, after 12–14 hours of fasting, blood glucose was measured in conscious rats before (baseline) and then 10, 30, 60, 120, and 180 minutes after the administration of 3 g/kg glucose by oral gavage. Blood was obtained as described before and analyzed using a glucometer (One Touch® Ultra, Lifescan, Johnson & Johnson, Milpitas, CA).

For ITT, a dose of 0.5 UI/kg human insulin (Actrapid®, Novo Nordisk, Boulogne-Billancourt, France) was injected intraperitoneally in conscious, fed rats. This dosage was chosen after having tested the efficacy of intraperitoneal injection of different doses of insulin in the same rat model. Sampling was as for other tests and blood glucose measured by glucometer at baseline and then 10, 30, 60, 90, 120, and 180 minutes after insulin injection.

For plasma hormones measurements, blood from the tail of conscious rats was collected in EDTA tubes containing the GI preservative. After centrifugation at 3000 rpm at 4°C for 12 minutes, plasma was immediately separated and stored at –80°C until analyzed. Rat radioimmunoassay kits were used for measurement of insulin (Diagnostics Products Corporation, Los Angeles, CA) and GIP (Inter Science institute, Inglewood CA).

Plasma total cholesterol, triglycerides, and free fatty acids (FFA) were measured both after 12–14 hours fasting and in the fed condition. Analytical methods were as follows: 1) FFA: enzymatic method ACS-ACOD (Wako Chemicals, Dallas, TX); 2) triglycerides: enzymatic method GPO-PAP; (Roche Diagnostics); and 3) cholesterol: enzymatic method CHOD-PAP (Roche Diagnostics).

## Statistical Analysis

Data are expressed as mean  $\pm$  SD. Areas under curves were calculated by trapezoidal integration. Statistical analysis was performed using one-way analysis of variance and the

Student *t* test as appropriate. *P* values < 0.05 were considered to be statistically significant.

## RESULTS

Before treatments, there were no significant differences between groups in terms of weight, fasting glycemia, and glucose tolerance. The operative time for the sham operation was equivalent to that of GJB (Table 1).

### Fasting Glycemia

GJB markedly reduced fasting plasma glucose levels. Mean plasma glucose 3 weeks postoperatively was  $96.3 \pm 10.1$  mg/dL, whereas mean preoperative values were  $159 \pm 47$  mg/dL (*P* = 0.01). The sham operation did not significantly change blood glucose levels, and glycemia remained consistently lower in the GJB rats with respect to sham-operated animals through the entire follow-up period (*P* = 0.02) (Fig. 3).

### OGTT

One week after surgery, glucose tolerance worsened in sham-operated animals, possibly as an effect of surgical stress. In sharp contrast, GJB strikingly improved glucose tolerance, (Fig. 4A) as demonstrated by a greater than 40% reduction of the area under blood glucose concentration curve (AUC; *P* < 0.001) as well as by lower mean 30-minute peak levels ( $203 \pm 67.6$  mg/dL vs.  $355.6 \pm 46.2$  mg/dL; *P* < 0.001) and lower mean 2-hour levels ( $134.1 \pm 31.4$  mg/dL vs.  $245.2 \pm 73.8$  mg/dL; *P* < 0.001). This effect was not achievable by food restriction because GJB rats showed markedly better glucose tolerance than rats undergoing diet (34% smaller AUC; *P* < 0.001) (Fig. 4B).

Although the improvement of glucose tolerance tended to weaken 4 weeks after the operation, GJB rats still had significantly lower 30-minute peaks and AUC values with respect to sham-operated animals at the test performed on the 36th postoperative week (Fig. 4C).

### Weight Gain and Food Intake

Despite the fact that GJB rats showed lower plasma glucose and better glucose tolerance than sham-operated animals as early as 1 week after treatment, the 2 groups had same average daily food intake (21 g/day for GJB rats vs. 20

g/day for sham animals) and no significant difference in weight gain profile during the first 3 months after surgery (Fig. 5A). Rats undergoing food restriction received a fixed amount of 8 g/day/rat of rat chow diet (*P* < 0.01) and showed greater weight loss than GJB rats (Fig. 5B).

### ITT

GJB rats had lower nadir levels of blood glucose ( $42 \pm 13$  vs.  $68 \pm 12$  mg/dL; *P* < 0.01) and smaller AUC (*P* < 0.05) than sham-operated controls, indicating better insulin sensitivity.

### Hormones Measurements

The GJB had no effect on basal plasma insulin but increased fasting plasma GIP ( $214 \pm 26.4$  postoperative vs.  $170 \pm 30.2$  preoperatively; *P* = 0.03); however, these levels were not significantly different than those of sham-operated rats.

### Lipid Profile

Sham operated GK rats showed similar plasma lipid levels compared with lean nondiabetic rats. In contrast, GJB rats had lower levels of FFA and cholesterol than both sham-operated animals and normal controls, the difference reaching statistical significance in the feeding state (Table 2).

### GJB Versus Rosiglitazone

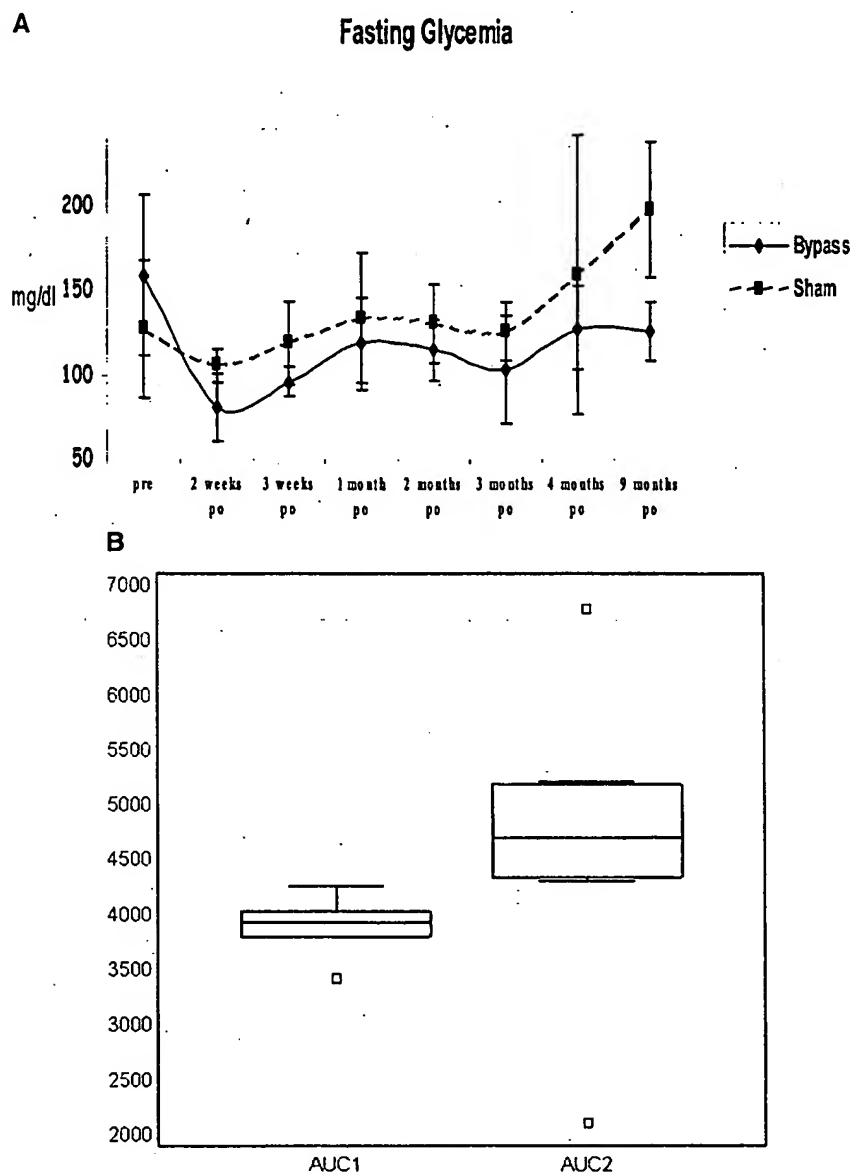
The calculated daily dose of rosiglitazone was 11.23 mg/kg. Compared with rosiglitazone, GJB resulted in lower fasting plasma glucose levels ( $86.4$  mg/dL  $\pm 26.3$  vs.  $119.8 \pm 7.9$  mg/dL; *P* = 0.01), similar degree of improvement of oral glucose tolerance, and better insulin sensitivity at the ITT (*P* < 0.05; Fig. 6).

## DISCUSSION

Our findings demonstrate that the bypass of the duodenum and jejunum reduces fasting glycemia and improves both glucose tolerance and insulin action in a nonobese animal model of type 2 diabetes. Our study allows several considerations. First, the control of diabetes induced by GJB is not dependent on the resolution of obesity-related abnormalities, because we used a nonobese model. The effect on glucose metabolism seems to be a direct consequence of the

TABLE 1. Preoperative Data

	GJB (n = 8)	Sham (n = 8)	Food restriction (n = 6)	Controls (n = 7)	<i>P</i>
Weight (g)	$335 \pm 21$	$338 \pm 38$	$332 \pm 9$	$330 \pm 6$	NS
Average diet (g/day)	23	23	24	25	NS
Fasting glycemia (mg/dL)	$159 \pm 47$	$126 \pm 40$	$135 \pm 21$	$121 \pm 6$	NS
OGTT (AUC)	$4733 \pm 13398$	$48910 \pm 7247$	—	$44356 \pm 5026$	NS
Operating time	$81 \pm 7$ min	$77 \pm 9$ min			NS

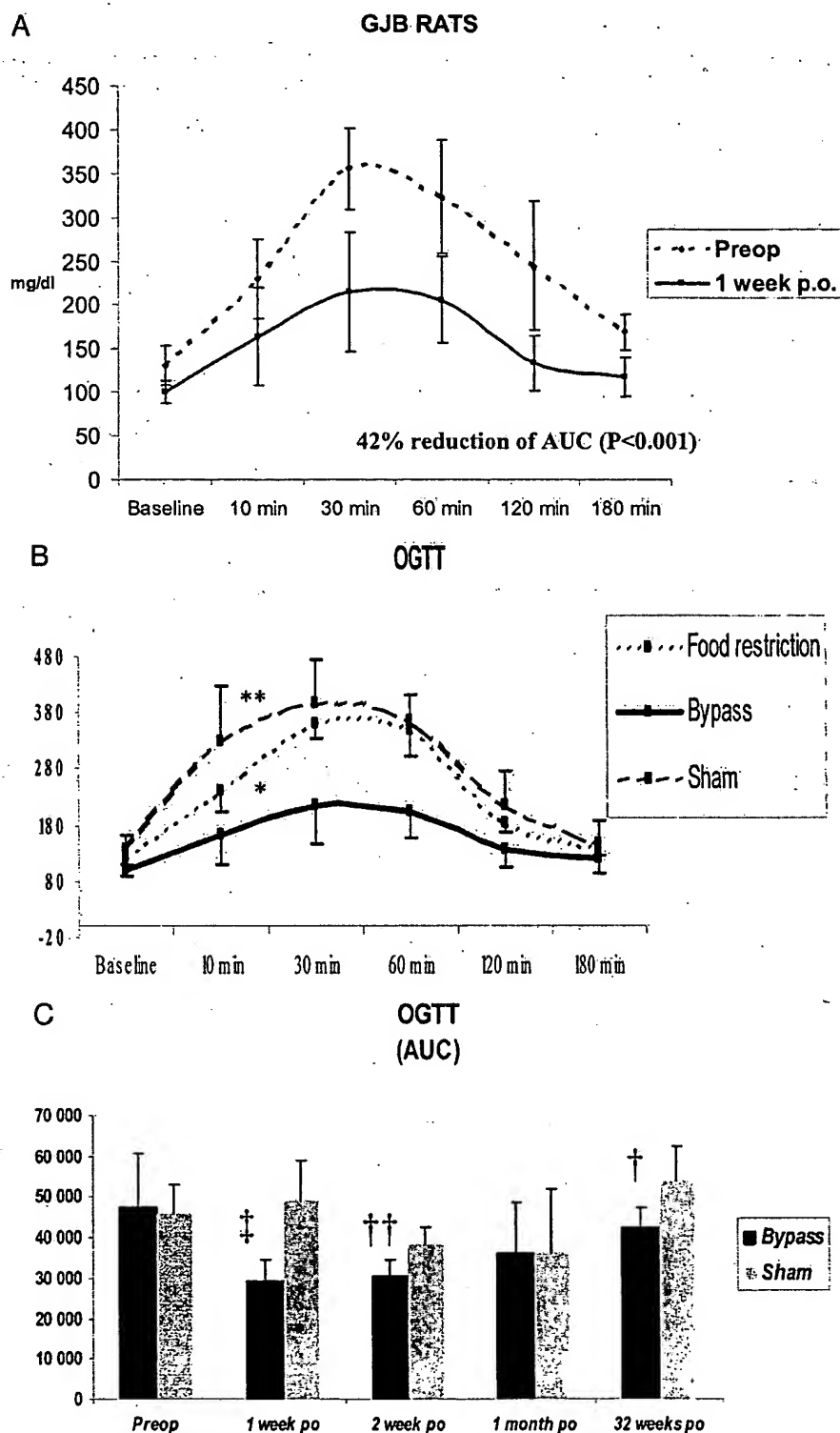


**FIGURE 3.** A, Mean fasting glycemia remained constantly lower in GJB rats compared with sham-operated animals. B, AUC indicates the area under the curve for fasting glycemia over the 36-week period of postoperative observation respectively in GJB rats (AUC1) and sham rats (AUC2);  $P = 0.02$ . (ANOVA)

duodenal jejunal exclusion rather than secondary to weight loss. Indeed, the study group and the sham-operated controls showed no significant differences in the weigh gain profiles whereas greater weight loss from food restriction did not result in the same degree of diabetes control as GJB in matched animals. Decreased food intake as a cause is also excluded by the same rates of food ingestion in GJB and sham operated animals and by the findings that animals submitted to greater restriction of food intake failed to achieve remarkable glycemic control.

The enhancement of insulin action after GJB has potential therapeutic relevance, as suggested by the fact that GJB improved fasting glycemia and insulin action more than rosiglitazone, a clinically effective thiazolidinedione drug whose efficacy has been documented in both obese and nonobese patients<sup>21</sup> as well as in several rodent models of type 2 diabetes.<sup>20</sup>

All together, our findings support the hypothesis that the control of diabetes observed in morbidly obese humans by means of RYGBP or BPD is caused by a direct antidiabetic



**FIGURE 4.** Glucose tolerance. A, OGTT performed in GJB rats 1 week after surgery showed a striking improvement of glucose tolerance, \*42% reduction of AUC;  $P < 0.001$ . B, GJB resulted in markedly better glucose tolerance compared to both sham operation and marked food restriction, \*GJB vs food restriction: 34% smaller AUC in GJB rats;  $P < 0.001$ . C, Glucose tolerance expressed as AUC under the glucose concentration curve during the 36 week follow-up period. † $P = 0.03$ ; †† $P = 0.02$ ; ‡ $P = 0.001$ .

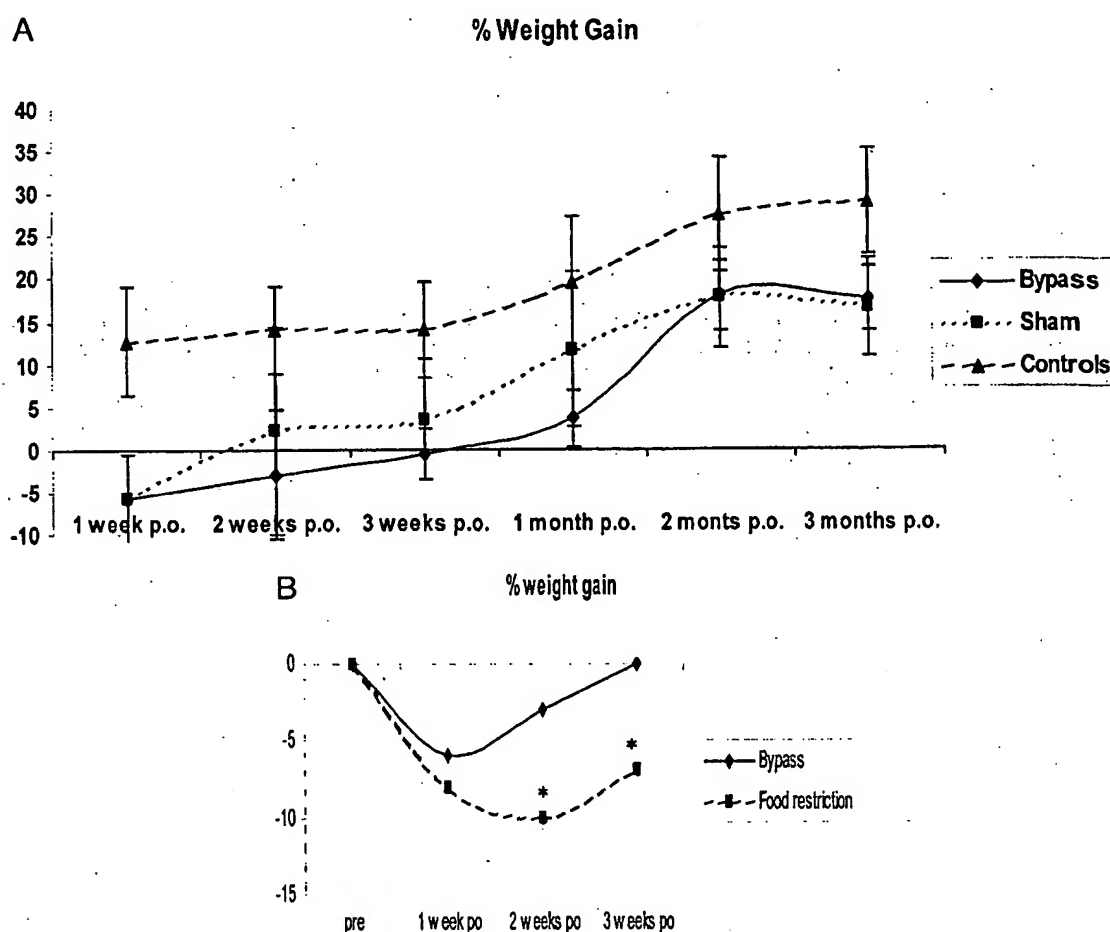
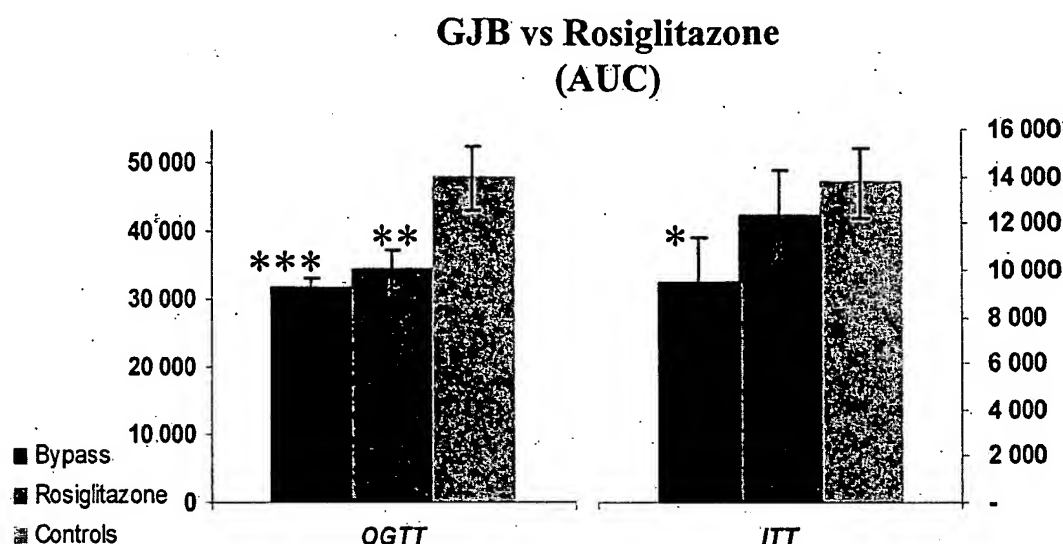


FIGURE 5. A, Both the GJB and the sham-operated group showed less weight gain compared with nonoperated controls ( $P < 0.05$ ); comparing the GJB group and the sham-operated animals, the difference in weight gain profile was not statistically significant. B, In contrast, food restriction induced significantly greater weight loss than GJB ( $*P < 0.05$ ).

TABLE 2. Lipids Profile (mmol/L)

	Cholesterol		TG		FFA	
	Fasting	Feeding	Fasting	Feeding	Fasting	Feeding
Bypass						
Mean	1.79	1.51	2.02	1	0.87	0.33
SD	0.3	0.28	1.24	0.63	0.27	0.14
Sham						
Mean	2.71	2.65	1.24	1.26	1.29	0.7
SD	0.44	0.42	0.31	0.35	0.4	0.18
Wistar (Normal, Lean)						
Mean	2.86	2.85	2.11	1.66	1.2	0.64
SD	0.57	0.57	0.88	0.64	0.21	0.16
Fasting vs, feeding			Fasting vs, feeding		By, vs, sham	P = 0.06 P = 0.001
Bypass	P = 0.03		Bypass	P = 0.04		
Sham	P = ns		Sham	P = ns		
Wistar	P = ns		Wistar	P = ns		



**FIGURE 6.** Rosiglitazone and GJB similarly improved glucose tolerance with respect to controls; however, GJB rats had better insulin sensitivity as demonstrated by lower 60-minute glucose levels ( $41 \pm 14$  vs.  $61 \pm 9$ ;  $P = 0.03$ ) and lower area under blood glucose concentration curve (AUC) at ITT (\*GJB vs Rosiglitazone:  $P < 0.05$ ; \*\*Rosigl. vs controls:  $P < 0.001$ ; \*\*\* GJB vs controls:  $P < 0.0001$ ).

effect of the operations. Our findings have also clinical and pathophysiologic implications.

### Mechanism of Action of Surgery

Our study pinpoints the exclusion of duodenum–jejunum as the factor responsible for control of diabetes. The exact molecular mechanism by which the duodenal–jejunal exclusion works, however, remains unclear. Pories et al were the first to theorize the possibility of endocrine changes as the mechanism by which RYGB improves diabetes.<sup>14</sup> This theory is based on the rationale that changes in the enteroinsular axis are possible because of the bypass of the gastric antrum along with the duodenum and jejunum.<sup>15</sup> More recently it was suggested that the control of diabetes could simply depend on duodenal–jejunal exclusion.<sup>5</sup> Intestinal lipid malabsorption resulting from the diversion of biliopancreatic juices into the terminal ileum has also been proposed as an alternative hypothesis for the control of diabetes after BPD.<sup>22</sup> The bypass of the proximal bowel may also reduce glucose absorption, which could, at least in theory, improve postprandial glucose levels.

Limitations of our study do not allow to establish which of these mechanisms is in cause. Indeed, we did not investigate intestinal absorption and, on the other hand, important changes of the dynamic of gastrointestinal hormones response to meal might have been overlooked by testing only fasting insulin and GIP as we did.

The low FFA levels found after GJB in this study might reflect depend on some degree of fat malabsorption and might

have played a role in improving glycemic control. Indeed, it is known that high levels of FFAs induce insulin resistance<sup>23</sup> and lowered FFAs are associated to improved insulin sensitivity in hyperlipidemic human subjects.<sup>24</sup>

However, it could be argued that inducing malabsorption of fat per se may not be the sufficient to explain control of diabetes in a normolipidemic animal model (as confirmed by our study's finding of similar lipid levels between sham operated rats and normal lean rats). It is entirely possible that the observed reduced FFA levels after GJB could also be the effect of improved insulin sensitivity secondary to other endocrine changes induced by the duodenal–jejunal bypass. In fact, it is known that improved insulin sensitivity lowers FFA levels.<sup>23</sup> Another possibility is that lowered FFAs may also be the result of increased leptin-induced intracellular fatty acid oxidation.<sup>25</sup> In fact, although leptin was not tested in the present study, several clinical observations showed that RYGB and BPD reduce leptin before weight loss<sup>26</sup> and independently on body fat content,<sup>27</sup> which suggest a surgically induced enhancement of leptin sensitivity.

The hypothesis of an endocrine effect consequent to the proximal bowel's bypass is also supported by several other observations. In humans, bypass procedures have been shown to produce substantial hormonal changes, including increased insulin-like growth factor 1 levels and decreased leptin, insulin, and GIP levels<sup>5</sup> even before body weight modifications.<sup>26</sup> Some have suggested that greater production of GLP-1, triggered by the earlier presentation of undigested food in lower segments of the bowel, might be involved in the



glycemic control consequent to bypass procedures for obesity surgery.<sup>28</sup>

In humans, RYGB seems to selectively reduce GIP levels of diabetic patients but not of nondiabetics.<sup>26</sup> Although the present study did not conclusively assess the effect of GJB on GIP, as we did not find significant differences between GJB rats and sham operated animals, the possibility of an effect of bypass procedures on GIP is of interest as defects in its signaling pathways are considered among the most critical alterations underlying type 2 diabetes, in which the incretin effect of GIP is characteristically attenuated<sup>18</sup> secondarily to decreased expression of GIP receptor.<sup>29</sup>

Considered along with the evidence of a defective enteroinsular axis in type 2 diabetes,<sup>18,29</sup> the results of our study support the speculation that the proximal gut plays a role in the etiology of the disease.<sup>5,15</sup> This hypothesis is also supported by the observation, apparently in contrast with our findings, that duodenal exclusion performed as part of the surgical treatment of gastric cancer in nondiabetic subjects impairs glucose tolerance rather than improving it.<sup>30</sup> Although this discrepancy may be explained by differences in the length of bowel bypass or by effects related to the presence of cancer, it is also suggestive for an aberrant signal originating in the proximal bowel of patients with type 2 diabetes but not in that of nondiabetic subjects.

We speculate that impairment of sensor/signaling mechanisms in the duodenal-jejunal tract, exacerbated by chronic overstimulation with nutrients (ie, high caloric diet) may trigger a diabetogenic signal responsible for impairment of insulin-signaling pathways and leading to insulin resistance and type 2 diabetes.

### Clinical Interest of a Surgical Treatment of Type 2 Diabetes

If surgery could also directly control diabetes in nonobese human subjects, would it be worthwhile to operate diabetic patients? Several observations suggest that implementing the current management of type 2 diabetes with alternative treatment strategies is suitable. In fact, the results of the United Kingdom Prospective Diabetes Study demonstrated the importance of lowering blood glucose to as near-normal levels as possible in patients with type 2 diabetes.<sup>31</sup> However, maintaining glycemic control in these patients is challenging. Very low calorie diets and weight loss programs rarely obtain substantial long-term benefit,<sup>13,32</sup> whereas oral antidiabetic agents have limitations and side effects.<sup>33</sup> Furthermore, insulin therapy has limited long-term efficacy in type 2 diabetes because of poor patient compliance to the regimen complexity and fear of weight gain and reduced quality of life.<sup>34</sup> In addition, glycemic control tends to deteriorate over time even after treatment.<sup>35</sup> The results of the Costs of Diabetes in Europe-Type 2 indicated that most

patients with type 2 diabetes have either poor or borderline glycemic control.<sup>36</sup>

In contrast, several series have clearly demonstrated effective long-term control of type 2 diabetes after RYGB and BPD in morbidly obese patients. In this special category of subjects, RYGB and BPD normalize glycemia, restore insulin sensitivity,<sup>7,15,22</sup> prevent the progression from impaired glucose tolerance to diabetes,<sup>15</sup> and also seem to reduce mortality from diabetes mellitus.<sup>37</sup> However, these results were achieved in patients with obesity-related diabetes or with severe hyperlipidemia and high circulating levels of FFA,<sup>22</sup> suggesting that they could have been a secondary effect of surgery as a result of induced weight loss and control of hyperlipidemic conditions. Our study now shows that the surgical bypass of the proximal bowel can also control type 2 diabetes in animals who lack both obesity and hyperlipidemia. This implies the important concept of duodenal-jejunal exclusion as a specific treatment of type 2 diabetes.

At the 1992 US National Institutes of Health consensus conference, recommendation was that individuals with a BMI greater than 35 kg/m<sup>2</sup> and type 2 diabetes should be considered for obesity surgery.<sup>38</sup> Although caution is mandatory when extrapolating the significance of animal data to human health, our experimental results suggest that even patients with BMI lower than 35 kg/m<sup>2</sup> and type 2 diabetes might benefit from surgery. This possibility stresses the need for clinical trials aimed to verify these findings in nonmorbidly obese humans.

Furthermore, our findings imply that morbidly obese patients with type 2 diabetes mellitus as a comorbidity might better benefit from bariatric procedures that include duodenal-jejunal exclusion (RYGB, BPD, or duodenal switch) rather than from simple gastroplasties.

As a "single-shot" kind of treatment, surgical management of type 2 diabetes might have several advantages over conventional therapies. First, long-term glycemic control would not be impaired by a patient's lack of compliance as it happens for diets, exercise, or complex medical regimens.<sup>34</sup> Moreover, a surgical treatment of type 2 diabetes could decrease the overall economic burden on health care systems by avoiding the costs of a life-long medical therapy. Tight blood glucose control is indeed associated with increased cost of intensive medical management<sup>39</sup> and therefore surgery might be a cost-effective option for the management of type 2 diabetes.

Of course, we would not wish to underestimate the risks of surgery. Recently published series of laparoscopic approach for RYGB documented an overall mortality of 0.2%,<sup>40</sup> whereas overall early complications range between 3 and 15%.<sup>40,41</sup> Because of possible iron and vitamin B12 deficiency, there is a need for long-term supervision and vitamin and mineral replacement. Large series documented a 0.4–0.8% mortality rate for BPD,<sup>7</sup> which is associated to a

variable but significant incidence of protein-calorie malnutrition, fat-soluble vitamin malabsorption, and osteoporosis.<sup>42</sup> However, reported mortality and morbidity of RYGB and BPD refer to surgery performed on patients with mean BMI in the low 50s, with some series including even patients with a BMI greater than 70 kg/m.<sup>2,41</sup> It seems reasonable that performing bypass surgical procedures in patients with lower BMIs might result in lower risk rates.

The findings of our study also suggest that a greater gastric volume than in standard RYGB could be preserved as well as distal diversion of biliopancreatic juices (as in BPD) could be avoided still maintaining efficacy on glycemic control. These technical variations may possibly reduce some of the long-term complications (ie, iron and vitamin B12 deficiency and protein malnutrition).

The risk of surgery should also be set against the risk of poorly controlled diabetes, which remains a devastating illness and whose long-term complications leads to retinopathy, nephropathy, neuropathy, and cardiovascular disease. Conceivably, the risk-benefit ratio might be best in overweight patients who do not respond to conventional treatment.

## CONCLUSIONS

Results of our study support the hypothesis that the bypass of duodenum and jejunum can directly control type 2 diabetes and not secondarily to the treatment of obesity, suggesting that surgery could also achieve glycemic control in nonmorbidly obese subjects. This study supports clinical trials aimed to verify these findings in human diabetes and to establish the possible role of surgery in the management of the disease. Our findings also stimulate further investigations on the role of the proximal bowel in the pathogenesis of type 2 diabetes, as this may lead to more targeted therapeutic approaches and possibly help us to understand the exact etiology of the disease.

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## REFERENCES

- Venkat Narayan KM, Gregg EW, Fagot-Campagna A, et al. Diabetes—a common, growing, serious, costly, and potentially preventable public health problem. *Diabetes Res Clin Pract.* 2000;50(Suppl 2):S77–S784.
- King H, Aubert RE, Herman WH. Global burden of diabetes, 1995–2025: prevalence, numerical estimates, and projections. *Diabetes Care.* 1998;21:1414–1431.
- Zimmet P, Alberti KG, Shaw J. Global and societal implications of the diabetes epidemic. *Nature.* 2001;414:782–787.
- Brolin RE. Update: NIH consensus conference. Gastrointestinal surgery for severe obesity. *Nutrition.* 1996;12:403–404.
- Rubino F, Gagner M. Potential of surgery for curing type 2 diabetes mellitus. *Ann Surg.* 2002;236:554–559.
- Marceau P, Hould FS, Simard S, et al. Biliopancreatic diversion with duodenal switch. *World J Surg.* 1998;22:947–954.
- Scopinaro N, Adami GF, Marinari GM, et al. Biliopancreatic diversion. *World J Surg.* 1998;22:936–946.
- Schauer PR, Ikramuddin S, Gourash W, et al. Outcomes after laparoscopic roux-en-Y gastric bypass for morbid obesity. *Ann Surg.* 2000;232:515–529.
- Cowan GS, Buffington CK. Significant changes in blood pressure, glucose, and lipids with gastric bypass surgery. *World J Surg.* 1998;22:987–992.
- Colditz GA, Willett WC, Rostitzky A, Manson JE. Weight gain as a risk factor for clinical diabetes mellitus in women. *Ann Intern Med.* 1995;122:481–486.
- Ford ES, Williamson DF, Liu S. Weight change and diabetes incidence: findings from a national cohort of US adults. *Am J Epidemiol.* 1997;146:214–222.
- Williamson DF, Thompson TJ, Thun M, et al. Intentional weight loss and mortality among overweight individuals with diabetes. *Diabetes Care.* 2000;23:1499–1504.
- Pinkney JH, Sjostrom CD, Gale EA. Should surgeons treat diabetes in severely obese people? *Lancet.* 2001;357:1357–1359.
- Pories WJ, Swanson MS, MacDonald KG, et al. Who would have thought it? An operation proves to be the most effective therapy for adult-onset diabetes mellitus. *Ann Surg.* 1995;222:339–350.
- Hickey MS, Pories WJ, MacDonald KG, et al. A new paradigm for type 2 diabetes mellitus: could it be a disease of the foregut? *Ann Surg.* 1998;227:637–643; discussion 643–644.
- D'Alessio D. Peptide hormone regulation of islet cells. *Horm Metab Res.* 1997;29:297–300.
- Dinneen SF. The postprandial state: mechanisms of glucose intolerance. *Diabet Med.* 1997;14(Suppl 3):S19–S24.
- Nauck MA, Heimesaat MM, Orskov C, et al. Preserved incretin activity of glucagon-like peptide 1 [7–36 amide] but not of synthetic human gastric inhibitory polypeptide in patients with type-2 diabetes mellitus. *J Clin Invest.* 1993;91:301–307.
- Galli J, Li LS, Glaser A, et al. Genetic analysis of non-insulin dependent diabetes mellitus in the GK rat. *Nat Genet.* 1996;12:31–37.
- Jucker BM, Schaeffer TR, Haimbach RE, et al. Normalization of skeletal muscle glycogen synthesis and glycolysis in rosiglitazone-treated Zucker fatty rats: an in vivo nuclear magnetic resonance study. *Diabetes.* 2002;51:2066–2073.
- Wagstaff AJ, Goa KL. Rosiglitazone: a review of its use in the management of type 2 diabetes mellitus. *Drugs.* 2002;62:1805–1837.
- Mingrone G, DeGaetano A, Greco AV, et al. Reversibility of insulin resistance in obese diabetic patients: role of plasma lipids. *Diabetologia.* 1997;40:599–605.
- Evans JL, Goldfine ID, Maddux BA, et al. Oxidative stress and stress-activated signaling pathways: a unifying hypothesis of type 2 diabetes. *Endocr Rev.* 2002;23:599–622.
- Lewis GF, Carpentier A, Adeli K, Giacca A. Disordered fat storage and mobilization in the pathogenesis of insulin resistance and type 2 diabetes. *Endocr Rev.* 2002;23:201–229.
- Shimabukuro M, Koyama K, Chen G. Direct antidiabetic effect of leptin through triglyceride depletion of tissues. *Proc Natl Acad Sci USA.* 1997;94:4637–4641.
- Rubino F, Gagner M, Gentileschi P, et al. The early effect of Roux-en-Y gastric bypass on hormones involved in body weight regulation and glucose metabolism. *Ann Surg.* 2004 (in press).
- de Marinis L, Mancini A, Valle D, et al. Plasma leptin levels after biliopancreatic diversion: dissociation with body mass index. *J Clin Endocrinol Metab.* 1999;84:2386–2389.
- Mason EE. Ileal [correction of ilial] transposition and enteroglucagon/GLP-1 in obesity (and diabetic?) surgery. *Obes Surg.* 1999;9:223–228.
- Lynn FC, Pamir N, Ng EH, et al. Defective glucose-dependent insulinotropic polypeptide receptor expression in diabetic fatty Zucker rats. *Diabetes.* 2001;50:1004–1011.
- Schwarz A, Buchler M, Usinger K, et al. Importance of the duodenal passage and pouch volume after total gastrectomy and reconstruction

- with the Ulm pouch: prospective randomized clinical study. *World J Surg*. 1996;20:60–66.
31. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet*. 1998;352:837–853.
32. Paasey RB, Frost J, Harvey P, et al. Five year results of a prospective very low calorie diet or conventional weight loss programme in type 2 diabetes. *J Hum Nutr Diet*. 2002;15:121–127.
33. Liebl A. Challenges in optimal metabolic control of diabetes. *Diabetes Metab Res Rev*. 2002;18(Suppl 3):S36–S41.
34. Evans A, Krentz AJ. Benefits and risks of transfer from oral agents to insulin in type 2 diabetes mellitus. *Drug Safety*. 1999;21:7–22.
35. DeFronzo RA. Pharmacologic therapy for type 2 diabetes mellitus. *Ann Intern Med*. 1999;131:281–303.
36. Liebl A, Neiss A, Spannheimer A. Costs of type 2 diabetes in Germany. Results of the CODE-2 study. *Dtsch Med Wochenschr*. 2001;126:585–589.
37. MacDonald KG, Long SD, Swanson MS, et al. The gastric bypass operation reduces the progression and mortality of non-insulin-dependent diabetes mellitus. *J Gastrointest Surg*. 1997;1:213–220.
38. National Institutes of Health Consensus Development Conference. Gastrointestinal surgery for severe obesity. *Am J Clin Nutr* 1992;55(2 Suppl):615S–619S.
39. Gray A, Raikou M, McGuire A, et al. Cost effectiveness of an intensive blood glucose control policy in patients with type 2 diabetes: economic analysis alongside randomised controlled trial (UKPDS 41). United Kingdom Prospective Diabetes Study Group. *BMJ*. 2000;320:1373–1378.
40. Gentileschi P, Kini S, Catarci M, Gagner M. Evidence-based medicine: open and laparoscopic bariatric surgery. *Surg Endosc*. 2002;16:736–744.
41. Schauer PR, Ikramuddin S. Laparoscopic surgery for morbid obesity. *Surg Clin North Am*. 2001;81:1145–1179.
42. Marceau P, Hould FS, Lebel S, et al. Malabsorptive obesity surgery. *Surg Clin North Am*. 2001;81:1113–1127.